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Pharmacological modulation of Alzheimer's beta-amyloid precursor protein levels in the CSF of rats with forebrain cholinergic system lesions.

Haroutunian V, Greig N, Pei XF, Utsuki T, Gluck R, Acevedo LD KL, Wallace WC.

Department of Psychiatry, Mount Sinai School of Medicine and B VA Medical Center, NY 10468, USA.

Abnormal deposition and accumulation of Alzheimer's amyloid b protein (A beta) and degeneration of forebrain cholinergic neuro among the principal features of Alzheimer's disease. Studies in r model systems have shown that forebrain cholinergic deficits ar accompanied by induction of cortical beta-amyloid precursor pr (beta-APP) mRNAs and increased levels of secreted beta-APP CSF. The studies reported here determined whether the CSF le secreted beta-APP could be altered pharmacologically. In differ experiments, rats with lesions of the forebrain cholinergic syste received injections of vehicle, a muscarinic receptor antagonist scopolamine, or one of two cholinesterase inhibitors - diisoprop phosphorofluoridate (DFP) or phenserine. Scopolamine was administered to determine whether the levels of beta-APP in th could be increased by anticholinergic agents. The cholinesteras inhibitors were administered to determine whether the forebrain cholinergic system lesion-induced increases in CSF beta-APP c reduced by cholinergic augmentation. Scopolamine administratio a significant increase in the CSF levels of secreted beta-APP in lesioned rats. Phenserine, a novel, reversible acetyl-selective cholinesterase inhibitor, significantly decreased the levels of se beta-APP in the CSF of forebrain cholinergic system-lesioned r whereas DFP, a relatively non-specific cholinesterase inhibitor, to affect CSF levels of secreted beta-APP. These results sugge the levels of secreted beta-APP in the CSF can be pharmacolog modulated but that this modulation is dependent upon the status forebrain cholinergic system and the pharmacological properties drugs used to influence it.

MeSH Terms:

- Alzheimer Disease/metabolism
- Amyloid beta-Protein Precursor/cerebrospinal fluid*
- Amyloid beta-Protein Precursor/drug effects*
- Animals
- Cholinesterase Inhibitors/pharmacology*
- Isoflurophate/pharmacology
- Male
- Muscarinic Antagonists/pharmacology
- Physostigmine/analogs & derivatives
- Physostigmine/pharmacology
- Prosencephalon/drug effects*
- Prosencephalon/metabolism*
- Rats
- Rats, Sprague-Dawley
- Scopolamine/pharmacology
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Substances:

- Amyloid beta-Protein Precursor
- Cholinesterase Inhibitors
- Muscarinic Antagonists
- phenserine
- Scopolamine
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- R01-AG10138/AG/NIA

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